of genes, the feasibility of mutation detection, and better understanding of the chain of events linking cause, process, and manifestations of (genetic) disease indicate that Garrod's vision was premature but correct. It is said that those who do not know or care for history may repeat it. In this excellent, at times beautiful, biography Bearn is giving us the chance not to repeat history or its mistakes but to build on it and proceed. The finest tribute we can pay to Garrod, short of reading his own works and putting into action his ideas, is to read *Archibald Garrod and the Individuality of Man* by Alexander G. Bearn.

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Preimplantation Diagnosis of Genetic Diseases: A New Technique in Assisted Reproduction. Edited by Y. Verlinsky, and A. M. Kuliev. New York: Wiley-Liss, 1993. pp. 155. $59.95.

PCR for amplifying specific DNA fragments has revolutionized many areas of molecular biology since it was first described almost 10 years ago. In prenatal diagnosis, for example, PCR is rapidly superseding techniques involving the hybridization of radiolabeled probes, because of its speed, versatility, and specificity—allowing, in many cases, direct detection of single-gene defects, without the use of radioactivity. It was an early report highlighting the sensitivity of PCR, however, that stimulated interest in the possibility of diagnosing inherited disease in the human embryo before implantation (Saiki et al. 1985). Conventional prenatal diagnosis by amniocentesis is usually carried out at 12–16 wk, and fetal amniocytes are usually cultured to increase numbers for genetic analysis. If the pregnancy is affected, however, the parents face the prospect of a termination at an advanced stage. The development of chorion villus sampling (CVS) has enabled diagnosis at much earlier stages of pregnancy, at 10–12 wk, and sufficient tissue is recovered for immediate DNA analysis, but termination is still the only option available if the pregnancy is affected. Diagnosis at preimplantation stages of development—or preimplantation diagnosis, using established methods for human in vitro fertilization (IVF) following superovulation—has the advantage that only unaffected embryos are selected for transfer, and any resulting pregnancy should be normal, thus avoiding the possibility of termination completely.

Progress with preimplantation diagnosis has been slow, reflecting the necessity of adequate preliminary studies on safety and accuracy of diagnosis. The first problem that had to be overcome was to develop methods for removing one or more cells from the early embryo for genetic analysis, without affecting viability or causing fetal abnormalities. One approach is to remove or biopsy some of the outer trophectoderm cells at the blastocyst stage. Effectively, this is the equivalent of a very early CVS, since these cells contribute only to the placenta, and the inner cell mass from which the fetus is derived is not affected. The principal advantages, therefore, are that the risk of affecting fetal development is minimized and that several cells can be recovered from each blastocyst. However, less than half of all human embryos develop to the blastocyst stage after IVF, reducing the possibility of identifying unaffected embryos for transfer.

An alternative is to biopsy embryos at earlier cleavage stages, and it is with this approach that preimplantation diagnosis has been successful clinically. At these stages, the cells of the mammalian embryo remain totipotent, and if a few are removed, the embryo is able to compensate without causing abnormal development. Fortunately, the human embryo appears to be no exception, since transfer of partially fragmented or degenerate embryos during routine IVF has not resulted in increased fetal abnormalities, and none have been reported so far after preimplantation diagnosis. The disadvantage is that only one or two cells can be removed from an embryo at about the 8-cell stage without affecting its viability. Given the extraordinary sensitivity of PCR, however, this has not proved to be a major problem, and a variety of unique sequences related to single-gene defects can now be amplified reliably from single cells.

The first pregnancies following preimplantation diagnosis were established in couples at risk of X-linked recessive disease. In these cases, PCR was used to amplify a Y-specific repeat sequence to identify potentially affected males so that only female embryos were returned to the uterus. To date, at least four centers have attempted preimplantation diagnosis, with a combined total of nearly 20 pregnancies, including, recently, several following diagnosis of the predominant ΔF508 deletion causing cystic fibrosis and one following diagnosis of a defect in the HPRT gene causing Lesch-Nyhan syndrome. Although clinical experience is limited, it seems that pregnancy rates among these predominantly fertile couples are likely to equal or even exceed those among infertile couples, which average 25%–35% per embryo transfer.

Verlinsky and his colleagues at the Reproductive Genetics Institute of Illinois Masonic Hospital, in Chicago, have been pioneers of this new technology in the United States, and it is therefore appropriate that one of the first books on the subject should come from them. The book is comprehensive in its coverage and includes all aspects, from specific indications for preimplantation diagnosis, detailed methodologies for micromanipulation, DNA analysis by PCR, and cytogenetics to a brief discussion of the ethical and legal issues. As such, it will be valuable to those considering applying these techniques—providing them with practical guidance and an introduction to the relevant literature. However, since this volume was written so early in the development of these techniques, when only the first handful of pregnancies had been established, it is doubtful whether it will convince clinical geneticists that this approach is sufficiently established to provide a credible alternative to the more conventional options for prenatal diagnosis. This is unfortunate, since more recent achievements make the outlook for preimplantation diagnosis more promising, as already discussed. On the other hand, the inclusion of detailed methodologies may give some readers the misleading impression that these protocols are universally accepted and established, when in fact they really represent work in progress, from only one of the centers attempting these diagnoses. There have already been several misdiagnoses. It is vital therefore that those contemplating offering this service are made fully aware of the difficulties and the experimental nature of this clinical treatment at this early stage. Indeed, until we have much more experience, it will remain necessary to counsel patients that they should consider confirmation of the diagnosis by CVS.

One approach unique to this group is preconception diagnosis of maternal defects by analysis of the first polar bodies of unfertilized oocytes. Clearly, excluding analysis of the paternal genetic contribution to each embryo is a serious limitation; however, this approach does avoid ethical objections to the manipulation of fertilized embryos. Diagnosis is based on the assumption that, in a carrier, the normal and mutant alleles segregate during the first meiotic division so that identification of one allele in the polar body implies that the other has segregated to the oocyte itself. The problem is that recombination (which occurs with a frequency related to the distance between the gene being analyzed and the centromere) results in copies of both alleles segregating to both the polar body and the oocyte. The genotype of the oocyte after fertilization and completion of the second meiotic division, therefore, cannot be predicted. Consequently, the proportion of oocytes in which a diagnosis can be obtained is reduced, and this probably explains the lack of success so far, since optimal pregnancy rates require the transfer of at least two unaffected embryos.

Although the initial stimulus came from the application of PCR to single-gene defects, recent attention has switched to the possibility of using cytogenetic methods to diagnose chromosomal abnormalities. It is well established that in the human there is a high incidence of aneuploidy at conception, which arises both during gametogenesis and early embryogenesis and which in many cases results in spontaneous abortion. The ability to detect aneuploidy and other chromosomal abnormalities may thus not only prevent affected pregnancies, if the abnormality is compatible with development to term, but may also reduce miscarriage rates, especially in older women. The chapter by A. Dyban, P. De Sutter, and Y. Verlinsky on cytogenetic analysis of polar bodies, oocytes, and embryos is, therefore, of particular interest. Andrei Dyban is renowned for his expertise in the cytogenetic analysis of mouse oocytes and embryos, but his publications in the former Soviet Union have often been overlooked. He had, in fact, succeeded in sexing mouse embryos by bisecting them and using one half for cytogenetic analysis before transferring the other half to recipients, over 10 years ago. However, the characteristics of mouse and human embryos are very different. Conventional cytogenetic analysis of human embryos has proved very difficult, and this is not sufficiently emphasized in this book. It is for this reason that the newer techniques for FISH are being used to detect chromosomes in interphase nuclei, and this work, which has considerable potential for detection of chromosomal defects, is only briefly mentioned. Dual FISH with X- and Y-specific probes has been used successfully for identifying the sex of embryos in X-linked recessive disease and is providing important information on the incidence of sex-chromosome mosaicism. Also, hopes that analysis of second polar bodies treated with okadaic acid to induce chromosome condensation may allow screening for aneuploidies (most of which occur during female meiosis) may not be fulfilled. Recent observations have indicated that, rather than nondisjunction, premature division of the centromere in meiosis I may be responsible for many aneuploidies (Angell 1991). In that event, polar-body analysis would not allow reliable prediction of the karyotype of the oocyte.

Preimplantation diagnosis remains far from being an established method for prevention of inherited disease, and this book, perhaps inevitably, does not go far enough to counteract the impression that it is. Nevertheless, recent experience

is promising, with success in screening for cystic fibrosis and Lesch-Nyhan syndrome, pregnancy rates of about one in three, and an increasing number of reports of successful diagnosis from single cells. With care, it should be possible to diagnose accurately almost any gene defect that has been characterized at the DNA level. This is an enormous challenge for the future—not least because of the need to come to terms with the ethical issues raised by some of the potential applications, including, for example, predisposition to heart disease or inherited cancers.

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